Review Article

Luteal insufficiency in first trimester

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ABSTRACT

Luteal phase insufficiency is one of the reasons for implantation failure and has been responsible for miscarriages and unsuccessful assisted reproduction. Luteal phase defect is seen in women with polycystic ovaries, thyroid and prolactin disorder. Low progesterone environment is created iatrogenically due to interventions in assisted reproduction. Use of gonadotrophin-releasing hormone analogs to prevent the LH surge and aspiration of granulosa cells during the oocyte retrieval may impair the ability of corpus luteum to produce progesterone. Treatment of the underlying disorder and use of progestational agents like progesterone/human chorionic gonadotrophin have been found to be effective in women with a history of recurrent miscarriage. There has been no proved beneficial effect of using additional agents like ascorbic acid, estrogen, prednisolone along with progesterone. Despite their widespread use, further studies are required to establish the optimal treatment. Literature review and analysis of published studies on luteal phase support.

Key words: Assisted reproduction, human chorionic gonadotrophin, luteal phase support, miscarriage, progesterone

Introduction

Luteal phase is the period between ovulation and either establishment of pregnancy or onset of menstrual cycle 2 weeks later. Following ovulation, the luteal phase of a natural cycle is characterized by the formation of corpus luteum, which secretes steroid hormones estrogen and mainly progesterone.[1] Embryonic implantation occurs during the implantation window where perfect synchronization of embryonic and endometrial signals are essential. Following implantation, the developing blastocyst secretes human chorinic gonadotrophin (HCG). Role of HCG is to maintain function of corpus luteum.[2] Luteal phase insufficiency is due to inadequate production of progesterone. Progesterone is essential for secretory transformation of the endometrium that permits implantation as well as maintenance of early pregnancy.[3] Luteal phase defect is one of the reasons for implantation failure, which has been responsible for many cases of miscarriages and unsuccessful assisted reproduction.[4]

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Physiology of Corpus Luteum

Studies have shown that surgical excision of corpus luteum (luteoctomy) before 7 weeks of gestation, uniformly precipitated an abrupt decrease in serum progesterone concentration followed by miscarriage.[5] The estimated onset of placental steroidogenesis occurs on the fifth gestational week. Transfer of luteal support to placenta occurs between seventh and ninth week and progesterone production from both sources continues to varying extent during the time period known as luteal-placental shift.[6] Progesterone secretion by the corpus luteum is required absolutely for the success of early human pregnancy. Progesterone not only supports the endometrial growth but also improves the blood flow and oxygen supply by increasing the nitric oxide production.[7,8] It keeps the myometrium quiescent by the utero relaxing effect.[9] They also potentially sustain the survival of the embryo by shifting the immune system towards production of T-helper (Th2) response.[10,11]

The size of corpus luteum remains relatively constant for the first 8-9 weeks of pregnancy followed by a marked regression from 10 week onwards.[12] Active angiogenesis occurs after the ovulatory LH surge and corpus luteum becomes one

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of the most highly vascularized organ in the body which is important for development and maintenance of luteal function. Adequate blood flow provides luteal cells with large amount of cholesterol that are needed for synthesis and delivery of the progesterone to the circulation.[13]

Tamura, *et al.*,[14] in their study have investigated the changes in the corpus luteum blood flow during the luteal phase and early pregnancy. The relatively high resistance index (RI) during the late follicular phase declined with progression towards the luteal phase. By the midluteal phase the RI was low, thus indicating a high blood flow to the corpus luteum. There was an increase in RI and therefore reduction in the blood flow on regression of the corpus luteum. In women with luteal phase defect the RI was significantly higher thus indicating a decrease in the blood flow. During pregnancy the RI remains at low mid luteal phase level for the first 7-8 weeks and then increases once the corpus luteum regresses. This early period, from luteal phase until around 8-10 weeks of pregnancy is the period during which interventions are likely to be successful.[14]

The proper function of the GnRH pulse generator in the hypothalamus is essential for normal ovarian function, hence also for the proper function of corpus luteum. Approximately one-half of luteal phase deficiencies are due to improper function of the GnRH pulse generator. Following ovulation the increased serum progesterone levels suppress the GnRH pulse generator, resulting in too few LH pulses and improper luteal function. Our increasing knowledge of auto and paracrine mechanisms between nonsteroidogenic and steroidogenic cells now allow subclassification of luteal phase defects of ovarian origin. Small luteal cells are LH responsive. If they develop improperly, the regularly occurring LH pulses are unable to stimulate progesterone secretion from small luteal cells which results in small luteal cell defect. Large luteal cells may also function improperly. Hence, basal progesterone release is too low while LH-stimulated progesterone release from the small luteal cells appears to be intact. This subclassification of luteal phase deficiency results in the suggestion of different treatments. In cases where the corpus luteum is LH-responsive, such as the hypothalamic corpus luteum insufficiency and the large luteal cell defect, HCG treatment or pulsatile treatment with GnRH is advisable. In the case of LH/hCG-unresponsive small luteal cell defect a progesterone substitution is suggested.[15]

Rationale for Luteal Support in Pregnancy

Placental human chorionic gonadotropin and corpus luteum secretion of progesterone and estradiol are the main endocrine events at the beginning of pregnancy, whilst the luteo-placental shift is an important step during the later stages. Progesterone not only affects decidualization, but is the major immunological determinant and controls uterine contractibility and cervical competence. These properties all contribute considerably towards the correct development of pregnancy and delivery at term.[16]

Successful pregnancy is associated with a down regulation of Th1 cytokines such as IFN-γ and TNF-α and an upregulation of Th2 cytokines such as IL-4, IL-6 and IL-10.[17] During pregnancy, progesterone stimulates the production of 34-KDa protein progesterone-inducing blocking (PIBF), which prevents inflammatory reactions toward the trophoblast via blockade of natural killer cell degranulation and an increase in asymmetric noncytotoxic-blocking antibodies.[18] Mitogen-stimulated peripheral blood mononuclear cells from women with a normal first trimester pregnancy have been shown to have significantly higher concentration of Th2 cytokines and lower concentration of Th1 cytokines than those from a women with a history of unexplained recurrent spontaneous miscarriage.[19] However, when PMBCs from women with recurrent spontaneous miscarriage were incubated with progesterone or dydrogestrone, the production of Th1 cytokines was inhibited and production of Th2 cytokines was increased, thus shifting the Th1 : Th2 balance in favor of pregnancy.[20]

PCOS women showed extremely low progesterone production in early pregnancy which might result in degenerative changes in early fetal growth.[21]

Rationale for Luteal Support in Assisted Reproductive Technology

Low progesterone environment is created iatrogenically due to interventions in assisted reproductive technology (ART):

- GnRH analogs, both agonist and antagonists are widely used to synchronize early follicular development and to prevent premature luteinization and ovulation during ovarian stimulation with gonadotrophins for IVF.[22] Long acting GnRH agonists have a two phased action. Initially they stimulate gonadotrophins release directly, but continued stimulation ultimately downregulates pituitary GnRH receptors and thereby suppresses gonadotrophins secretion. Once downregulated pituitary function does not resume until 2-3 weeks after end of GnRH therapy.[23] As corpus luteum function is dependent on pituitary LH stimulation, luteal phase support is considered prudent to prevent any progesterone deficiency that might jeopardize the success of implantation or early pregnancy.[23,24]
- The GnRH antagonist blocks the pituitary GnRH

receptors directly but for a shorter duration than the agonist and also predisposes to poor luteal function, regardless of whether recombinant LH, HCG or a GnRh agonist is used to trigger ovulation.[25]

- HCG administered for final oocyte administration suppresses the LH production via a short loop feedback mechanism.[26]
- Supraphysiological levels of steroids secreted by a high number of corpora lutea during the early luteal phase directly inhibit the LH release via the negative feedback mechanism at the hypothalamopitutary axis level.[27]
- Removal of large amount of granulosa cells during oocyte retrieval might diminish the most important source of progesterone synthesis. However, this hypothesis was disproved when it was established that the aspiration of a preovulatory oocyte in a natural cycle neither diminished the luteal phase steroid secretion nor shortened the luteal phase.[28]
- Luteal phase LH levels were found to be reduced in HMG only cycles, which also indicates that defective LH secretion might induce a luteal phase defect in stimulated cycles.[29]

Detecting Luteal Phase Insufficiency

Serum progesterone level of less than 3 ng/ml is consistent with follicular phase levels. To confirm ovulation, values at midluteal phase should be atleast 6.5 ng/ml and preferably 10 ng/ml or more. There is often poor correlation with the histological state of the endometrium.[30] There are no reliable methods for diagnosis of progesterone deficiency during luteal phase or early pregnancy. Progesterone secretion is pulsatile. Blood levels range from 2 to 40 ng/ml within a brief time period. Blood levels are not reliable for determining the need for or effect of luteal support. There is no consensus on minimum serum progesterone concentration that defines luteal function. Random serum progesterone levels are difficult to interpret beyond documenting ovulation. Endometrial biopsy is no longer the gold standard for assessment of endometrial maturation.[31]

Pharmacokinetics

Various formulations of progesterone oral and parenteral are available. Oral progesterone undergoes first pass prehepatic and hepatic metabolism. It results in progesterone degradation to 5α and 5β metabolites.[32] Serum levels typically return to baseline in 6 hours when administered orally. Vaginally administered progesterone yields lower serum levels, but achieve endometrial tissue concentrations upto 30-fold greater than those achieved with intramuscular progesterone.[33] The levels remain elevated for up to 48 hours vaginally due to countercurrent exchange in progesterone transport between the anatomically closed blood vessels.[34] Intramuscular progesterone results in a higher plasma concentration and level is maintained for a longer duration.[33]

A meta-analysis on the route of administration of luteal phase support showed a comparable effect between vaginal progesterone as a capsule or bioadhesive gel and intramuscular progesterone administration on the endpoints of clinical pregnancy (OR-0.91,95% CI 0.74-1.31) and ongoing pregnancy.(OR-0.94,95% CI 0.71-1.26)

A nominally significantly lower rate of miscarriage was observed with vaginal progesterone compared with intramuscular progesterone.[35]

Additional agents with Progesterone

Ascorbic acid

It is a water-soluble antioxidant that has been associated with fertility.[36] Ascorbate depletion leads to generation of reactive oxygen species which inhibits the action of LH and blocks steroidogenesis.[37] Women with unexplained infertility have a lower antioxidant status in their peritoneal fluid.[38] Griesinger, *et al.*, conducted a prospective randomized placebo-controlled study to evaluate the role of ascorbic acid as additional support during luteal phase. There was no clinical evidence of any beneficial effect as defined by ongoing pregnancy rate, in stimulated IVF cycles regardless of the dose used.[39]

Prednisolone

The rationale behind this approach has been that embryos might be exposed to bacteria or leukocyte infiltration if the protective coating of the zona pellucida is breached. Immunosuppression caused by the glucocorticoids would decrease the presence of peripheral lymphocytes. But in a prospective randomized study by Ubaldi, *et al.*, did not find any beneficial effect of adding low dose prednisolone to progesterone during the luteal phase.[40]

Aspirin

It acts by inhibitng the enzyme cyclooxygenase, thus avoiding prostaglandin synthesis.

Aspirin has been shown to increase the uterine blood flow.[41] A prospective randomized study was done to test whether adjuvant therapy with ASA and prednisolone could improve the outcome of IVF. It was shown that the combination could improve the ovarian responsiveness but does not significantly improve the pregnancy and the implantation rate.[42]

Estrogen

The implantation process depends on the quality of

endometrium, which is affected by both estrogen and progesterone. The role of estrogen during the luteal phase is unclear.

Under progesterone supplementation it has been shown that midluteal E2 levels decrease in a proportion of patients and this might be associated with concomitant decrease in pregnancy rates. A systematic review and meta-analysis was performed to examine whether the probability of pregnancy increased by adding estrogen to progesterone for luteal support. Four RCTs were included. No statistically significant differences were present between patients who received a combination of progesterone and estrogen, when compared with those who received only progesterone for luteal support in terms of positive HCG rate, clinical pregnancy rate and live birth rate per woman randomized. The currently available evidence suggests that addition of estrogen to progesterone in the luteal phase does not increase the probability of pregnancy. However, a large multicenter trial is needed to further clarify the role.[43]

Human Chorinic Gonadotrophin

HCG acts as an indirect form of luteal support by stimulating the corpus luteum. It increases the concentration of estrogen and progesterone thus rescuing the failing corpora lutea.[44] Administration of HCG has also shown to increase the concentrations of placental protein 14,[45] integrin and relaxin which have been shown to increase at the time of implantation.[46]

In the latest meta-analysis conducted by Nosarka, *et al.* (2005), 18 randomized trials were evaluated. Luteal support with either HCG or progesterone was associated with a significantly higher pregnancy rate compared with no support. In subanalysis of five trials, HCG appeared superior to progesterone (n = 438, OR-1.71, 95% CI 1.06-2.76).The disadvantage of using HCG as a luteal support stems from its potential for increasing rates of ovarian hyperstimulation syndrome (OHSS). Several trials have shown a statistically significant higher rate of moderate or severe OHSS in women receiving HCG. The risk was estimated to be twice higher than progesterone.[47]

Supplementation of Luteal Support in Early Pregnancy

Progesterone is known to induce secretory changes in the lining of the uterus essential for successful implantation of a fertilized egg. It has been suggested that a causative factor in many cases of miscarriage may be inadequate secretion of progesterone. Therefore, progestogens have been used, beginning in the first trimester of pregnancy, in an attempt to prevent spontaneous miscarriage. In order to determine the efficacy and safety of progestogens as a preventative therapy, a meta-analysis was performed of randomized or quasi-randomized controlled trials comparing progestogens with placebo or no treatment given in an effort to prevent miscarriage. Searches were performed using the Cochrane Pregnancy and Childbirth Group's Trials Register (January 2008), CENTRAL (The Cochrane Library 2006, Issue 4), MEDLINE (1966 to June 2006), EMBASE (1980 to June 2006), CINAHL (1982 to June 2006), NHMRC Clinical Trials Register (June 2006) and Meta-Register (June 2006).

Fifteen trials (2118 women) were included. The meta-analysis of all women, regardless of gravidity and number of previous miscarriages, showed no statistically significant difference in the risk of miscarriage between progestogen and placebo or no treatment groups (OR) 0.98; 95% confidence interval (CI) 0.78 to 1.24) and no statistically significant difference in the incidence of adverse effect in either mother or baby. In a subgroup analysis of three trials involving women who had recurrent miscarriages (three or more consecutive miscarriages), progestogen treatment showed a statistically significant decrease in miscarriage rate compared to placebo or no treatment (OR 0.38; 95% CI 0.20-0.70). No statistically significant differences were found between the route of administration of progestogen (oral, intramuscular, vaginal) versus placebo or no treatment.

There is no evidence to support the routine use of progestogen to prevent miscarriage in early to midpregnancy. However, there seems to be evidence of benefit in women with a history of recurrent miscarriage. Treatment for these women may be warranted given the reduced rates of miscarriage in the treatment group and the finding of no statistically significant difference between treatment and control groups in rates of adverse effects suffered by either mother or baby in the available evidence. Larger trials are currently underway to inform treatment for this group of women.[48]

For the PCOS patients with episodes of early pregnancy loss, progesterone supplementation, if low at 5-weeks gestation, during early pregnancy period might restore the fetal growth and then avoid recurrent miscarriages.

PCOS women are thought to have the higher possibility in early pregnancy loss than non-PCOS patients. A study done to clarify the relation between corpus luteum function and early pregnancy loss in PCOS women showed no significant difference in progesterone and estrogen concentration in the mid secretory phase. The progesterone production in 5-week pregnancy, on the other hand, demonstrated a remarkable

change; 27.5 ± 10.8 ng/ml (Mean ± SD) in PCOS group and 32.4 ± 14.3 ng/ml in control respectively ($P < 0.05$). In addition, PCOS women with early pregnancy loss demonstrated lower progesterone production at 5-week gestational stage than those without miscarriage. Serum testosterone level did not affect corpus luteum function in both mid secretory and early pregnancy stage. Thus for the PCOS patients with episodes of early pregnancy loss, progesterone supplementation, if low at 5 weeks gestation, might restore the fetal growth and then avoid recurrent miscarriages.[21]

The mechanism explaining the association between first-trimester spontaneous miscarriages and the presence of thyroid autoimmunity remains unclear. Hypothesis states that glycoprotein hormone receptors have a significant structural similarity. Cross-reactivity between chorionic gonadotropin (hCG), thyroid-stimulating hormone (TSH) and their receptors (R) is suggested by the thyrotropic action of hCG during pregnancy. If TSH can activate LH/CG-R then, the TSH-R blocking autoantibodies could bind and block LH/CG-R in the corpus luteum through a similar cross-reactivity process. This inhibition could lead to a decrease in steroid hormones production, essential for the support of pregnancy during the first trimester and result in spontaneous miscarriages. No evidence is present to confirm the hypothesis.[49]

Hyperprolactinemia is associated with corpus luteal insufficiency. Therefore, treatment with dopaminergic drugs and progesterone supplementation in them is necessary.[15]

Duration of Progesterone Supplementation

Transfer of luteal support to placenta occurs between the seventh and ninth weeks. Progesterone withdrawal before the seventh week will lead to pregnancy loss. After detecting fetal heart tones, endogenous progesterone levels are sufficient. The optimal duration of supplementation has not been established. A recently published study looked specifically at a shorter protocol in which progesterone was being stopped on the day of pregnancy test versus 6 weeks until ultrasound confirmation of pregnancy. No differences were observed in pregnancy or live birth rates.[50] Frozen embryo transfer and donor oocyte cycles are replacement cycles, with supplementation typically lasting until a gestational age of 10 weeks.[31]

Summary

- Progesterone is essential for secretory transformation of the endometrium that permits implantation as well as maintenance of early pregnancy.
- Luteal placental shift occurs between 7 and 9 weeks of pregnancy. The early period, from luteal phase until around 8-10 weeks of pregnancy is the period during which interventions are likely to be successful.
- There are no reliable methods for diagnosis of luteal insufficiency during luteal phase of menstrual cycle or during early pregnancy.
- Progesterone supplementation is beneficial in women with history of recurrent miscarriages.
- I ART cycles involving use of a GnRH agonists or antagonists, progesterone supplementation yields higher pregnancy rates.
- Luteal phase HCG is associated with an increased risk of OHSS.

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